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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/706,635	11/12/2003	Richard W. Moyer	UF-221C1XCZ1	8304

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EXAMINER	
WEHBE, ANNE MARIE SABRINA	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 04/08/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/706,635	MOYER ET AL.	
	Examiner	Art Unit	
	Anne Marie S. Wehbe	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 December 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5 and 7-18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *14-17* is/are allowed.

6)☒ Claim(s) *1-5,7-13 and 18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendment and response received on 12/16/04 has been entered. Claims 6 has been canceled and new claims 17-18 have been added. Claims 1-5, and 7-18 are pending and under examination in the instant application. An action on the merits follows.

Those sections of Title 35, US code, not included in this action can be found in the previous office action.

Double Patenting

The rejection of claims 1-6, and 8-15 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 14-21 of U.S. Patent No.6,106,825, the rejection of claims 1-10, and 12-16 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-11 and 21 of U.S. Patent No. 6,127,172, and the rejection of claims 1-10, and 12-16 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 76-85, 88-89, and 101-102 of copending Application No. 09/662,254, are all withdrawn in view of applicant's submission of terminal disclaimers over these patents and application on 12/16/04.

Claim Rejections - 35 USC § 112

The rejection of previously pending claims 1-16 under 35 U.S.C. 112, first paragraph, for scope of enablement, stands over newly amended claims 1-5, 7-13, and 18. Applicant's

arguments and the declaration by Dr. Moyer under 37 CFR 1.132 have been fully considered but have not been found persuasive in overcoming the instant grounds of rejection for reasons of record as discussed in detail below.

In view of applicant's declaration and supporting evidence, the scope of enablement has been modified as follows: the specification, while being enabling for a method of *in vitro* delivery of a gene to a vertebrate cell comprising infecting or transfecting cells with a recombinant entomopox vector or virus comprising a polynucleotide operably linked with a heterologous early pox promoter sequence or a non-pox promoter sequence activated by the cellular RNA polymerase of the cell, does not reasonably provide enablement for *in vivo* methods of gene delivery to vertebrate cells using these entomopox viruses or vectors such that therapeutically effective amounts of protein encoded by the polynucleotides are expressed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.
The applicant argues that a "therapeutic effect" is not recited by the instant claims and that both early pox virus promoters and non-pox virus promoters can be utilized in rEPV vectors to deliver genes encoding proteins to a cell in vivo. While the claims as written do not specifically recite that the expression of protein encoded by the polynucleotide contained in the entomopox vector has a therapeutic effect, the specification clearly teaches that the intended use for methods of gene delivery *in vivo* is treatment of disease or conditions. The specification discloses that said recombinant entomopox viral DNA or viral particles can be used to infect, transfect, or transduce an animal wherein the expression of therapeutic amounts of the heterologous protein in the animal results in the amelioration of diseases or conditions caused by protein deficiencies or

abnormalities. As a preferred embodiment, the specification discloses that proteins such as interleukins, cytokines, enzymes, structural proteins, growth hormones and interferons can be expressed in a vertebrate animal using the recombinant entomopox viruses of the instant invention, wherein the amount of protein expressed is of therapeutic benefit to the animal (specification, pages 6 and 12). The specification does not identify other uses for the claimed *in vivo* methods of gene delivery. Therefore, based on the clearly set forth intended use of the methods of gene delivery in the specification, the issue of enablement for "therapeutic effect" is in fact relevant to the patentability of the claims.

The applicant further argues that while the prior art does not demonstrate therapeutic gene delivery to mammals using entomopox vectors, the prior art does teach gene delivery *in vivo* using other viral vectors, citing various patents and publications. It is noted that none of the cited references on page 9, paragraph 1, have been provided to the examiner for consideration or cited on an IDS, and as such the actual teachings of these references cannot be evaluated. Further, the previous office action made of record several review articles at or before the time of filing which clearly establish that the art at the time of filing did not consider the expression of therapeutic levels of a gene using currently available vectors to be either routine or predictable (see Verma et al., Marshall et al., Orkin et al., and Ross et al.).

In regards to the declaration by Dr. Moyer, the applicant argues that the declaration shows that the skilled artisan would expect that gene expression *in vivo* using the claimed entomopox vectors would be sustained for more than 2 days, particularly if non-pox virus promoters are used . The declaration by Dr. Moyer states that pages 75 and 81 of the instant specification demonstrate that non-pox virus promoters such as the CMV promoter and TK

promoter can used to express a heterologous selectable marker from rEPV in mammalian cells in vitro. Page 75 of the instant specification teaches how to construct an rEPV comprising CMV and TK promoters operably linked to marker genes. Page 85 of the specification teaches that the rEPV disclosed on page 75 can infect cells *in vitro* and that after multiple rounds of selection, cells expressing both marker genes can be detected. Expression from non-poxvirus promoters requires the participation of cell based factors rather than entomopox factors, as such, both the specification and the art teach that expression using promoters such as CMV or HSV-TK requires the integration of the recombinant EPV DNA into the host cell's genome such that it is accessible to host transcription factors. The applicant's data clearly demonstrates that integration following infection with rEPV is not a high percentage event such that detection of cells which may express the recombinant protein of interest requires several rounds of selection to increase the number of cells with the integrated DNA. The specification fails to provide sufficient guidance as to dosages or routes of administration of rEPV which utilize non-pox virus promoters to vertebrates such that rEPV DNA integrates into the host's cells *in vivo* and results in detectable amounts of protein expression. Further, the specification does not provide any guidance as to methods of selecting for cells with integrated EPV DNA *in vivo* such that the expression of the heterologous gene can be detected *in vivo*. Thus, based on the mechanism of expression of a heterologous gene from an rEPV using a non-pox virus promoter, the lack of guidance provided by the specification for dosages, routes of delivery, and selection methods for expressing detectable amounts of protein *in vivo* by administering rEPV encoding a heterologous protein under transcriptional control of any non-pox virus promoter, and the breadth of the

claims, it would have required undue experimentation to practice the scope of the instant invention as claimed.

In regards to the argument that cell specific non-pox promoters could further improve gene expression, especially in lymphoid cells, it is noted that the specification does not teach this embodiment nor disclose any cell specific promoters. Further, in regards to the publications cited on page 10 of the response, it is noted that only abstracts for the Qin et al. and Nettelbeck et al. references have been provided. None of the other references have been provided for the examiner's consideration and as such their teachings cannot be evaluated. Regarding Qin et al. and Nettelbeck et al., it is noted that both articles appear to support the position of the office that therapeutic gene expression is difficult and unpredictable. The Qin et al. abstract states that, "one of the major limitations to current gene therapy is the low-level and transient vector gene expression due to poorly defined mechanisms, possibly including promoter attenuations or extinction." (Qin et al., abstract). Nettelbeck et al. also states that, "A large number of highly specific promoters has been described, but their applicability is often hampered by their inefficient transcriptional activity" (Nettelbeck et al., abstract). Neither reference appears to solve these difficulties, nor do either reference teach how cell specific promoters might behave in the context of entomopox virus vectors. As such, the applicant's arguments are not persuasive.

The applicant also argues that transient gene expression can be therapeutically useful, citing Baumgartner et al. and Manning et al. Manning et al. examines the possibilities of using immunosuppression to allow readministration of recombinant AAV vectors. Manning et al. does not teach or suggest that this strategy could be useful for entomopox vectors, nor that entomopox vectors and AAV vectors share similar properties when administered *in vivo*. As such, a nexus

between the teachings of Manning et al. and the instant invention cannot be found. In regards to Baumgartner et al., Baumgartner et al. teaches the intramuscular injection of plasmid DNA encoding VEGF and observes gene expression up to 8 weeks which correlated with a therapeutic effect on critical limb ischemia. As discussed in detail in the previous office action, the single example of *in vivo* delivery of entomopox virus vector reported in the specification resulted in the detectable expression of lacZ in the muscle on day 2. There is no evidence that the expression of lacZ from the entomopox vector would continue up to 8 weeks. Further, plasmid vectors are not viral vectors, and thus, the skilled artisan would not find a nexus between results obtained using plasmid vector and results obtained using a viral vector such as entomopox. Finally, while Baumgartner et al. showed that the level of VEGF expression obtained over the 8 weeks correlated with a therapeutic effect, there is no similar showing in applicant's example, nor any evidence that the entomopox vectors are capable of expressing a similar level of gene expression *in vivo* as seen with the plasmid vectors used by Baumgartner et al. Therefore, in view of the quantity of experimentation necessary to determine the parameters affecting gene delivery, particularly viral dosage and the site and routes of administration, the lack of direction or guidance provided by the specification concerning these and other issues listed above, the absence of working examples which demonstrate the expression of therapeutic levels of a protein following *in vivo* delivery of the disclosed entomopox virus vectors, the breadth of the claims, and the unpredictable and undeveloped state of the art with respect to *in vivo* gene expression and gene therapy, it would have required undue experimentation for the skilled artisan to deliver a therapeutically effective amount of a protein to a vertebrate animal using the entomopox virus and vectors of the instant invention.

Claims 14-17 are considered free of the prior art of record and allowable at this time.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Wehbé, Ph.D., whose telephone number is (571) 272-0737. The examiner can be reached Monday- Friday from 9:30-6:00 EST. If the examiner is not available, the examiner's supervisor, Ram Shukla, can be reached at (571) 272-0735. For all official communications, **the new technology center fax number is (571) 273-8300**. For informal, non-official communications only, the examiner's direct fax number is (571) 273-0737.

Dr. A.M.S. Wehbé

ANNE M. WEHBE' PH.D
PRIMARY EXAMINER